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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JAY A. BERZOFSKY, MASAKI TERABE,
and SO MATSUI

Appeal 2010-011270
Application 10/532,374
Technology Center 1600

Before TONI R. SCHEINER, LORA M. GREEN, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to a method for inhibiting recurrence of a tumor. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

Statement of the Case

Background

The Specification teaches "methods of preventing tumor recurrence. More specifically, the disclosure relates to methods of blocking transforming growth factor (TGF)-β signaling in order to inhibit the immunosuppressive effects of TGF-β thereby preventing the recurrence of a tumor" (Spec. 1, ll. 10-14).

The Claims

Claims 46-72 are on appeal. Claim 46 is representative and reads as follows:

> 46. A method of inhibiting recurrence of a tumor in a subject, comprising:
>
> administering a therapeutically effective amount of a monoclonal antibody obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849), or a humanized equivalent thereof, to the subject in order to block an immunosuppressive effect of transforming growth factor (TGF)- β in the subject, wherein the subject is at risk for recurrence of the tumor, and wherein the monoclonal antibody or humanized antibody is specific for TGF-β and neutralizes an activity of TGF-β, thereby inhibiting recurrence of the tumor in the subject.

The issues

A. The Examiner rejected claims 46-50, 52-55, 59-67, 69, and 71 under 35 U.S.C. § 103(a) as obvious over Dasch,[2] Sukhatme,[3] Barbera-Guillem,[4] Rosenblum,[5] and Zavada[6] (Ans. 3-5).

B. The Examiner rejected claims 46-55 and 59-72 under 35 U.S.C. § 103(a) as obvious over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, Zavada, and Suthanthiran[7] (Ans. 6-7).

C. The Examiner rejected claims 46-72 under 35 U.S.C. § 103(a) as obvious over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, Zavada, and Terabe[8] (Ans. 7-8).

A. 35 U.S.C. § 103(a) over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada

The Examiner finds that Dasch teaches "methods for treating tumor cells by administering monoclonal antibodies reactive to TGF-beta to suppress the immunosuppressive effects of TGF-beta and to permit generation of an immune response against the tumor and this results in

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[2] Dasch et al., US 6,090,383, issued Jul. 18, 2000.
[3] Sukhatme, V., WO 00/01410 A1, published Jan. 13, 2000.
[4] Barbera-Guillem, E., US 6,224,866 B1, issued May 1, 2001.
[5] Rosenblum, M., US 2005/0214307 A1, published Sep. 29, 2005.
[6] Zavada et al., US 6,297,041 B1, issued Oct. 2, 2001.
[7] Suthanthiran et al., US 2004/0197333 A1, published Oct. 7, 2004.
[8] Terabe et al., *NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway*, 1 NATURE IMMUNOLOGY 515-520 (2000).

tumor regression . . . The preferred monoclonal antibody is Mab 1 D11.16" (Ans. 4).

The Examiner finds that it "is known in the art that compounds that treat tumors can also be used to treat tumor recurrence . . . Barbera-Guillem discloses that one skilled in art would readily recognize that the same procedure used for treating a cancer would also be used for the treatment of recurrence of the same cancer" (*id.*). The Examiner finds that "Rosenblum discloses that the same antibody used in treatment of tumors is used in the treatment of tumor recurrence (paragraph [0043]). Zavada et al discloses the same compounds (which include polypeptides and antibodies) can be used for treatment and treatment of recurrence" (*id.* at 5).

The Examiner finds it "obvious to one of ordinary skill in the art at the time of applicant's invention to use the antibody of the primary reference in the treatment of tumor recurrence" (*id.*).

Appellants "emphasize that the claims are directed to methods of *inhibiting* a tumor *recurrence* and not to methods of *treating* a tumor or *treating* a tumor *recurrence*, and that treating and inhibiting are two very different actions" (App. Br. 6). Appellants "strenuously submit[ ] (and maintain) that the specification does not define *treatment* as being equivalent to *inhibition*, nor should the Office interpret that Applicants believe that these terms are equivalent" (*id.* at 7).

Appellants contend that "it is well known in the art that 'the effectiveness of an agent for *treating* a tumor recurrence does not predict the effectiveness of the same agent for *inhibiting* the recurrence' (June 5, 2009 Declaration at paragraph 3; see also June 5, 2009 Declaration at paragraphs

5 and 6)" (App. Br. 8). Appellants "respectfully submit that the teachings of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* could not have been combined to predictably yield the claimed invention" (*id.* at 12). Appellants also contend that "one of skill in the art would not have had a reasonable expectation of success, based on the disclosures of Barbera-Guillem, WO 00/01410, Zavada *et al.*, or Rosenblum, that the 1D11.16 antibody disclosed in Dasch *et al.* or its humanized equivalent could be used to inhibit tumor recurrence" (*id.* at 16).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the combination of Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada render the claims obvious?

Findings of Fact

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

1. The Specification teaches that:

> Treatment: Refers to both prophylactic inhibition of disease (such as tumor recurrence) and therapeutic interventions to alter the natural course of an untreated disease process, such as a tumor growth. Treatment of a tumor includes, for instance, the surgical removal of the tumor. Treatment of a tumor can also include chemotherapy, immunotherapy, or radiation therapy. Two or more methods of treating a tumor can be provided to a subject in combination. Treatment of a subject includes inhibiting or measurably reducing the recurrence of a tumor.

(Spec. 17, ll. 11-16.)

2. The Specification teaches that the "term 'inhibits' does not require absolute inhibition. Similarly, the term 'prevents' does not require absolute prevention. Reducing a recurrence of a tumor includes reducing the recurrence of a tumor by measurable amounts, for example at least 5%, at least 10%, at least 20%, at least 30% . . ." (Spec. 17, ll. 31-33).

3. Dasch teaches a "method for treating tumor cells that produce TGF-B, by administering a therapeutically effective amount of a monoclonal antibody reactive with TGF-B to suppress the immunosuppressive effects of TGF-B" (Dasch, col. 2, ll. 28-32).

4. Dasch teaches that the "MAb of this invention may be administered to block TGF-B's immunosuppressive effects (to permit the generation of an immune response against the tumor), and result in tumor regression" (Dasch, col. 5, ll. 54-58).

5. Dasch teaches that "[s]everal preferred murine monoclonal antibodies have been produced according to the present invention. Monoclonal antibody 1D11.16 (IgGi) refers to the MAb produced by a clone of the murine hybridoma cell line 1D11.16" (Dasch, col. 5, ll. 18-21).

6. Sukhatme teaches that "the inhibition of TGF-β-mediated angiogenesis results in the inhibition of tumor growth . . . inhibition of TGF-β -mediated angiogenesis can result in regression of established tumors. Tumor regression can be determined as described herein" (Sukhatme 22, ll. 25-29).

7. Sukhatme teaches that the

> inhibition of TGF-β-mediated angiogenisis can be accomplished in a number of ways. For example, the proliferating cells (*e.g.*, tumor cells) can be contacted with

> molecules that inhibit TGF-β-mediated angiogenic activity. For example, an antibody that inhibits or neutralizes TGF-β activity can be used to render the TGF-β ineffective. Appropriate antibodies, including monoclonal antibodies, are described in U.S.Pat. No. 5,571,714[9]

(Sukhatme 23, ll. 1-6).

8. Sukhatme teaches that an

> effective amount of the TGF-β antagonist is an amount sufficient to inhibit the angiogenesis which results in the disease or condition, thus completely, or partially, alleviating the disease or condition. Alleviation of the angiogenesis-mediated disease can be determined by observing an alleviation of symptoms of the disease, *e.g.*, a reduction in the size of a tumor, or arrested tumor growth.

(Sukhatme 28, ll. 13-18.)

9. Sukhatme teaches that "the term 'effective amount' also means the total amount of each active component of the composition or method that is sufficient to show a meaningful patient benefit, *i.e.*, treatment, healing, prevention or amelioration of the relevant medical condition" (Sukhatme 28, ll. 18-21).

10. Barbera-Guillem teaches that "[t]umor markers (e.g., CEA and CA19.9) found in the peripheral blood may also be used to assess status of the tumor during and after treatment" (Barbera-Guillem, col. 23, ll. 18-20).

11. Barbera-Guillem teaches that "[a]s will be apparent to one skilled in the art, essentially the same procedures outlined above (for treatment of an individual having residual colorectal cancer with liver

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[9] We note that Dasch is a continuation based on this patent.

metastases) may be used to treat an individual for treatment of recurrence of colorectal tumor with liver metastases" (Barbera-Guillem, col. 23, ll. 20-25).

12. Rosenblum teaches

> a method of treating proliferative cell diseases characterized by tumors expressing an antigen to which ZME antibody binds, comprising administration of a cytocidally effect dose of the composition of claim 1 to an individual in need of said treatment. In another embodiment, the present invention involves a method of treating melanoma comprising administration of a gelonin coupled monoclonal antibody directed to ZME antigen to an individual having melanoma. In yet another embodiment of the present invention, there is provided a method of preventing recurrence of melanoma tumors comprising administration of gelonin conjugated monoclonal antibody ZME to an individual diagnosed as having a tumor bearing ZME tumor associated antigen.

(Rosenblum 3 ¶ 0043.)

13. Zavada teaches that a use for the "vaccine would be to prevent recidivism and/or metastasis. For example, it could be administered to a patient who has had an MN-carrying tumor surgically removed, to prevent recurrence of the tumor" (Zavada, col. 11, ll. 5-9).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

Analysis

Claim interpretation

Claim construction is a legal issue which is reviewed *de novo*. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc).

The Examiner and Appellants dispute the interpretation of the term "treatment." While the Specification expressly states that "[t]reatment of a subject includes inhibiting or measurably reducing the recurrence of a tumor" (Spec. 17, ll. 15-16; FF 1), none of the independent claims uses the word "treatment."

Instead, claims 46, 60, and 63 are independent claims directed to methods of "inhibiting recurrence of a tumor" or "enhancing an activity of an immune cell to inhibit recurrence of a tumor" comprising either "administering" or "contacting" a patient with a monoclonal antibody of 1D11.16. These claims also incorporate wherein clauses where administration of the antibody results in "inhibiting recurrence of the tumor in the subject" (Claim 46).

The wherein clauses do not inform the mechanics of how the "administering" or "contacting" steps are performed; rather, the wherein clauses merely characterize the result of that step. Therefore, the wherein clause is not entitled to weight in construing the claims. *Cf. Minton v. National Assoc. of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) ("The term 'efficiently' [in the whereby clause] on its face does not inform the mechanics of how the trade is executed . . . . Rather, the term

'efficiently' is a laudatory one characterizing the result of the executing step.").[10]

We therefore interpret each of the claims as requiring the administration of the monoclonal antibody 1D11.16 to a subject at risk for recurrence of a tumor.

Obviousness

Claim 46

Dasch teaches a "method for treating tumor cells that produce TGF-B, by administering a therapeutically effective amount of a monoclonal antibody reactive with TGF-B to suppress the immunosuppressive effects of TGF-B" (Dasch, col. 2, ll. 28-32; FF 3). Dasch teaches that the "MAb of this invention may be administered to block TGF-B's immunosuppressive effects (to permit the generation of an immune response against the tumor), and result in tumor regression" (Dasch, col. 5, ll. 54-58; FF 4).

Dasch does not expressly recognize that the subject population may include those with recurrent tumors (*see* Ans. 4).

Sukhatme, citing to a parent application of Dasch's, teaches that "proliferating cells (e.g., tumor cells) can be contacted with molecules that

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[10] The claim interpreted in *Minton* read, in pertinent part:
"1. A method for trading securities between individuals, comprising: . . . executing a trade of the security based on information contained in the offer for consideration specified in the reply to the offer, *whereby the security is traded efficiently between the first [offering] individual and the second [replying] individual; . . . .*" *Minton*, 336 F.3d at 1380 (emphasis in original).

inhibit TGF-β-mediated angiogenic activity. For example, an antibody that inhibits or neutralizes TGF-β activity can be used to render the TGF-β ineffective. Appropriate antibodies, including monoclonal antibodies, are described in U.S.Pat. No. 5,571,714" (Sukhatme 23, ll. 1-6; FF 7).

Barbera-Guillem teaches that "[a]s will be apparent to one skilled in the art, essentially the same procedures outlined above (for treatment of an individual having residual colorectal cancer with liver metastases) may be used to treat an individual for treatment of recurrence of colorectal tumor with liver metastases" (Barbera-Guillem, col. 23, ll. 20-25; FF 11).

Rosenblum teaches "a method of preventing recurrence of melanoma tumors comprising administration of gelonin conjugated monoclonal antibody ZME to an individual diagnosed as having a tumor bearing ZME tumor associated antigen" (Rosenblum 3 ¶ 0043; FF 12).

We conclude that the express teachings of Barbera-Guillem and Rosenblum which suggest that antibodies known to be effective treatments for tumors may also be useful in inhibiting recurrence of tumors would have reasonably suggested using the tumor treating antibody of Dasch to inhibit the recurrence of tumors.

Appellants contend that "it is well known in the art that 'the effectiveness of an agent for *treating* a tumor recurrence does not predict the effectiveness of the same agent for *inhibiting* the recurrence' (June 5, 2009 Declaration at paragraph 3; see also June 5, 2009 Declaration at paragraphs 5 and 6)" (App. Br. 8). Appellants "respectfully submit that the teachings of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.*

could not have been combined to predictably yield the claimed invention" (*id.* at 12).

We are not persuaded. We have considered the Berzofsky Declaration,[11] which states that "it would not be obvious to one of skill in the art that the same agent can be effective at both treating a tumor recurrence and inhibiting (preventing) a recurrence" (Berzofsky Dec. 4 ¶ 8).

However, Dasch expressly teaches that the 1D11.16 antibody functions to treat tumors and results in tumor regression (FF 3-5). More importantly, Barbera-Guillem and Rosenblum teach that administration of antibodies which cause tumor regression will also result in inhibition of tumor recurrence (FF 10-12). In particular, Barbera-Guillem directly contradicts the Berzofsky Declaration when stating that "[a]s will be apparent to one skilled in the art, essentially the same procedures outlined above (for treatment of an individual having residual colorectal cancer with liver metastases) may be used to treat an individual for treatment of recurrence of colorectal tumor with liver metastases" (Barbera-Guillem, col. 23, ll. 20-25; FF 11). As we balance this evidence, we agree with the Examiner that the prior art reasonably suggests that antibodies effective against tumors will have efficacy against recurrence of these tumors (FF 10-12).

Appellants also contend that "one of skill in the art would not have had a reasonable expectation of success, based on the disclosures of Barbera-Guillem, WO 00/01410, Zavada *et al.*, or Rosenblum, that the

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[11] Declaration of Dr. Jay A. Berzofsky, submitted June 5, 2009.

1D11.16 antibody disclosed in Dasch *et al.* or its humanized equivalent could be used to inhibit tumor recurrence" (App. Br. 16).

We are not persuaded. Dasch teaches that the 1D11.16 antibody would be expected to function in the treatment of tumors (FF 4-5). Both Barbera-Guillem and Rosenblum teach that antibodies against tumors would be reasonably expected to have efficacy in preventing tumor recurrence (FF 10-12). We note that the Specification recognizes that a 5% reduction in recurrence satisfies the inhibition requirement (FF 2). *Kubin* stated that "[r]esponding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court [in *O'Farrell*] stated: '[o]bviousness does not require absolute predictability of success … *all that is required is a reasonable expectation of success*.'" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)).

The instant treatment has a greater expectation of success than either Barbera-Guillem or Rosenblum since the target of 1D11.16 is TGF-β, not the tumor itself. That is, while the antibodies of Barbera-Guillem or Rosenblum might be specific for antigens which mutate or change to resist the agent, as discussed in the Berzofsky Declaration (*see* Berzofsky Dec. 3 ¶ 6), TGF-β is less likely to experience a functional change so the 1D11.16 antibody to TGF-β will continue to "suppress the immunosuppressive effects of TGF-β" (Dasch, col. 2, ll. 31-32; FF 3).

Claims 60 and 63

Appellants acknowledge that the claim elements "are an inherent property of the 1D11.16 antibody" (App. Br. 17). Appellants reiterate the

argument that none of the prior art "is predictive of Applicants use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence" (*id.*). Appellants argue that none of the prior art references disclose "a method of enhancing an activity of an immune cell to inhibit recurrence of a tumor using the 1D11.16 antibody" (*id.* at 18).

We remain unpersuaded for the reasons given above. Appellants correctly note that treatment of a tumor with the 1D11.16 antibody would inherently result in "enhancing an activity of an immune cell." The Examiner finds that Dasch teaches that the antibody blocks "TGF-B's immunosuppressive effects (to permit the generation of an immune response against the tumor), and result in tumor regression" (Dasch, col. 5, ll. 54-58; FF 4). Further, treatment with the same antibody on the same patient population will inherently yield the same results. *See In re Best*, 562 F.2d 1252, 1255 (CCPA 1977) ("Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product.").

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada render the claims obvious.

B. 35 U.S.C. § 103(a) over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, Zavada, and Suthanthiran

The Examiner finds it obvious "to use 1D11.16 to treat cancers of the breast, lung, small intestine (reads on gastrointestinal), colon, kidney, ovary, prostate, brain, pancreas, skin, bone, uterus, testicles, cervix and liver" (Ans. 7).

The Examiner provides sound fact-based reasoning for combining the method of Suthanthiran with Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada (*see* Ans. 6-7). We adopt the fact finding and analysis of the Examiner as our own. Appellants argue the underlying obviousness rejection over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada, but Appellants do not identify any material defect in the Examiner's reasoning for combining Suthanthiran with Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada. Since Appellants only argue the underlying rejection which we affirmed above, we affirm this rejection for the reasons stated by the Examiner.

C. 35 U.S.C. § 103(a) over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, Zavada, and Terabe

The Examiner finds "in view of the known use of the assays for tumor immunosurveillance and in view of the fact that the primary reference calls for monitoring tumor progression, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use these assays to monitor tumor progression" (Ans. 7-8).

The Examiner provides sound fact-based reasoning for combining the method of Terabe with Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and

Zavada (*see* Ans. 7-8). We adopt the fact finding and analysis of the Examiner as our own. Appellants argue the underlying obviousness rejection over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada, but Appellants do not identify any material defect in the Examiner's reasoning for combining Terabe with Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada. Since Appellants only argue the underlying rejection which we affirmed above, we affirm this rejection for the reasons stated by the Examiner.

SUMMARY

In summary, we affirm the rejection of claims 46, 60, and 63 under 35 U.S.C. § 103(a) as obvious over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, and Zavada. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 47-50, 52-55, 59, 61, 62, 64-67, 69, and 71, as these claims were not argued separately.

We affirm the rejection of claims 46-55 and 59-72 under 35 U.S.C. § 103(a) as obvious over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, Zavada, and Suthanthiran.

We affirm the rejection of claims 46-72 under 35 U.S.C. § 103(a) as obvious over Dasch, Sukhatme, Barbera-Guillem, Rosenblum, Zavada, and Terabe.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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